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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,468	02/08/2002	Stephen J. Benkovic	P05537US1	9968

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EXAMINER

SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/071,468

Applicant(s)

BENKOVIC ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14 and 30-33 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 14 and 30-33 is/are rejected.
- 7) ☒ Claim(s) 30 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Applicant's response and amendment, received February 23, 2005, in response to the Office Action, mailed November 2, 2004, is acknowledged. It is acknowledged that applicants have cancelled Claims 15, 20, 21, and 24, amended Claim 14, and added Claims 30-33. Claims 14 and 30-33 are pending and are hereby reconsidered.

Examiner's note: The claim listing filed with the instant amendment lists the status of Claim 30 as amended. However, no prior claim listing presented a Claim 30. Therefore, Claim 30, of the instant amendment, is a new claim.

Oath-Objections

Objection to the Oath of April 18, 2002 for failing to provide the serial number and country code for the PCT application indicated as being filed February 8, 2002, is maintained. In support of their request that said rejection be withdrawn, Applicants state that they submitted an Oath on February 8, 2002 for the instant application which, in the first paragraph, claims priority to Provisional Application Serial No.: 60/267,440. However, the Oath of February 8, 2002, as found in the instant application, does not claims priority to Provisional Application Serial No.: 60/267,440. Therefore, objection to the Oath is maintained.

Claims-Objections

Claim 30 is objected to for improper antecedent usage. On line 7, "a" should be "the".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 14 and 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 14 and 30 introduce the limitation of “measuring an initial fluorescence activity in said cell to establish a baseline; introducing into said cell a nucleic acid construct having a sequence encoding a chimeric protein...and measuring a change in the fluorescence activity caused by proteolytic cleavage of said chimeric protein in said cell.” The specification fails to describe a method for detecting proteolytic cleavage of a fluorescent substrate wherein the fluorescent activity of a cell, prior to introduction of the nucleic acid molecule encoding the fluorescence chimeric protease substrate, is measured and used as a fluorescent baseline to analyze proteolysis of the fluorescence chimeric protease substrate. A person of ordinary skill in the art would know that an assay to measure cleavage of a fluorescent substrate must compare the fluorescence of the substrate in the presence and absence of an active protease. Comparing the fluorescence of the cell in the absence of the fluorescent substrate to the fluorescence of the cell in the presence of the fluorescent substrate is not appropriate. Therefore, Claims 14 and 30, as well as Claims 31-33, which depend from Claim 30, are rejected under 35 U.S.C. 112, second paragraph. For purposes of examination, it is assumed that Claims 14 and 30-33 are meant to recite comparing the fluorescence of the substrate in the presence and absence of an active protease, as disclosed in Figure 2.

Claim 33 is further rejected under 34 USC 112, second paragraph, for being dependent on itself. For purposes of examination, it is assumed that Claim 33 is dependent from Claim 32.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 14 and 30 introduce the limitation of “measuring an initial fluorescence activity in said cell to establish a baseline; introducing into said cell a nucleic acid construct having a sequence encoding a chimeric protein...and measuring a change in the fluorescence activity caused by proteolytic cleavage of said chimeric protein in said cell.” The specification fails to describe a method for detecting proteolytic cleavage of a fluorescent substrate wherein the fluorescence of a cell, prior to introduction of the nucleic acid molecule encoding the fluorescence chimeric protease substrate, is measured and used as a fluorescent baseline to analyze proteolysis of the fluorescent chimeric protease substrate. As such, introduction of said limitation is New Matter and Claims 14 and 30, as well as Claims 31-33, which depend from Claim 30, are rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

Rejection of Claim 14 under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998, for the reasons explained in the First Action on the Merits, mailed September 23, 2003, the Final Rejection, mailed March 10, 2004, and the RCE First Action Merits, mailed November 2, 2004, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

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(i) The suggestion to combine must come from the prior art and not from Applicant's specification or impermissible hindsight; neither Mahajan et al nor Abedi et al suggest to combine. One of skill in the art would not be motivated to combine Mahajan with Abedi.

(ii) The Examiner seems to be taking a very broad view of the disclosure in Abedi, stating that Abedi teaches a GFP as a scaffold for peptide *substrates* inserted within the GFP sequence. But Abedi et al never describes or even suggest the use of peptides as *substrates* in his library. Rather, Abedi et al teaches the production of a peptide-*aptamer* library designed to bind and, thus, identify target ligands. The present invention's problem to be solved, of assaying for proteolytic cleavage of a substrate, does not involve ligand discovery.

Reply:

(i) As clearly described in the Action of November 2, 2004, it is not necessary for either Mahajan et al nor Abedi et al to suggest to combine. The motivation to combine the teachings of Mahajan et al and Abedi et al to render obvious the instant invention is derived from the nature of the problem to be solved and the knowledge of persons of ordinary skill in the art (M.P.E.P 2143.01 [R-2]).

(ii) It is acknowledged that Abedi et al do not teach the use of GFP as a scaffold for peptide substrates. Abedi et al do teach the general use of GFP as a scaffold for inserting desired peptides. The lack in Abedi et al, of not teaching inserting protease substrates, is taught by Mahajan et al, as stated in the original rejection, mailed September 23, 2003. Mahajan et al, teach a method for assaying protease activity using a fluorescent substrate wherein a peptide substrate is inserted between two fluorescent proteins.

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Rejection of Claims 20, 21, and 24 under 35 U.S.C. 103(a), as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997 is withdrawn because said claims have been canceled. However, Claims 30-33 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997 and Grakoui et al, 1993 for the same reasons. The teachings of Mahajan et al and Abedi et al were described in the previous Office Action. Mahajan et al do not teach analysis of serine protease activity, as recited in Claim 30. However, serine proteases, including the NS3/4A protease, were well known in the art. It would have been obvious to a person of ordinary skill in the art to use the method devised from combining of Mahajan et al and Abedi et al, as described in the Action of September 23, 2003, to analyze the activity of serine proteases. Motivation to do so is provided by the desire to test for inhibitors of serine protease activity. For example, Martin et al teach designing inhibitors of NS3/4A, a hepatitis C virus serine protease as a means to develop anti-viral agents, which is a desirable and practical objective (Abstract). Martin et al further disclose a peptide substrate that is useful for measuring NS3/4A activity (pg 609, lines 2-3). One would also be motivated to compare the cleavage of the substrate with active and inactive NS3/4A in order to demonstrate the specificity of cleavage. Creating inactive variants of serine proteases by mutating the active site serine residue is well known in the art. For example, Grakoui et al, 1993 teach mutation of the active-site serine residue in NS3/4A to alanine; mutation to glycine would also be obvious to a person of ordinary skill in the art. The expectation of success is high, as fluorescent fusion protease substrates as well as a peptide substrate for the serine protease NS3/4A are known in the art. Therefore, Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over

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Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997 and Grakoui et al, 1993.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.

A handwritten signature in black ink, appearing to read 'P. Achutamurthy', with a long horizontal stroke extending to the right.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600